ESI Preprints **Not Peer-reviewed**

Current Perspectives in the Use of Phytotherapy for the Treatment of Breast Cancer

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Doi: 10.19044/esipreprint.3.2023.p156

Approved: 06 March 2023
Posted: 09 March 2023

Cite As:
Anago A.D., Segbo J.A.G., Gnangnon F., Akpovi C.D. & Agbangla C. (2023). *Current Perspectives in the Use of Phytotherapy for the Treatment of Breast Cancer*. ESI Preprints. https://doi.org/10.19044/esipreprint.3.2023.p156

Abstract

Breast cancer is the most commonly diagnosed cancer leading to death among women worldwide. However, there is a significant improvement in the treatment of breast cancer. Today, the conventional treatment of breast cancer combines surgery , chemotherapy, radiation, targeted therapy, hormone therapy and immunotherapy. Despite the advances in the diagnosis skills and in the treatment of breast cancer it has been observed that the recurrence rate experienced by breast cancer patients

is quite high. Moreover, the conventional treatment is often accompained with side effects. Thus, there is a need to search for new bioactive molecules. Plant derived natural compounds can play a major role as sources of new bioactive substances for the treatment of breast cancer. Many plants have been reported to have anti-breast cancer properties. While investigations are being made to demonstrate the cytotoxic activities of many plants, the use of phytomedicine is not generating fully attention by mainstream practitioners. Some significant results were observed by patients with breast cancer history by combining phytotherapy and the conventional medicines. Hence, plant extracts are more being used in the treatment of breast cancer as adjuvant therapy. In this review we will present a summary of the advances of the researches on the efficacity of phytotherapeutic products when discussing their use in the treatment of breast cancer.

Keywords: Breast cancer, phytotherapy, anti-breast cancer properties, plant extracts

Introduction

Of the 10 million new cases of invasive cancer world-wide each year in males and females combined, 10% arise in the breast, which makes it the second most common site of malignant neoplasms after the lung (Parkin et al., 2001). Currently, standard treatment protocol combines a multidisciplinary approach involving different therapies such as surgery, radiation, and medical oncology (i.e., chemotherapy, immunotherapy, and hormonal therapy) to obtain a local (i.e., remove or destroy cancer in the breast) or systemic (i.e., destroy or control cancer cells throughout the body) effects (Cortella & Pocheltino, 1993). But various types of chemotherapies fail due to adverse reactions, drug resistance, and target specificity of some types of drugs. Natural compound mixtures that are believed to have multiple specific targets with minimal acceptable side-effects are now of interest to many researchers due to their cytotoxic and chemosensitizing activities (Newman et al., 2003).

Plants have had an essential role in the folklore of ancient cultures. The expertise to select the right plants, methods of drug concoction and their specificuse has been first transferred orally from one generation to the next until set down (Kinghorn, 2001; Samuelsson, 2004). Over 50% of all modern clinical drugs are of natural product origin (Stuffness & doros, 1982) and natural products play an important role in drug development programmes of the pharmaceutical industry (Baker et al., 1995; Cordell 1995). The recognition of medicinal plants as effective and inexpensive sources of synthetic novel chemotherapeutic compounds is increasing in the last decades and many researchers focus their research on this promising area

(Omogbadegun, 2013). Today, it is estimated that about 25–28% of all modern medicines are directly or indirectly derived from higher plants demonstrating the enormous medicinal potential of plants that has been known for thousands of years in traditional medicine (Stuffness & Dorod, 1982; Chin et al., 2006). Furthermore, most of time, patients use plant products for self-medication. It uses products derived from all or parts of plants and is a common practice in all civilizations around the world including Asia, Africa, Europe, and America (Rossi et al., 2015). Herbal-based and plant-derived products can be hence exploited with sustainable comparative and competitive advantages, especially in developing countries to reduce the exorbitant cost of the breast cancer treatment. In this review, an overview of the currently use of phytotherapy in the treatment of breast cancer and a summary of some selected plants with anti- breast cancer properties will be presented.

1. Plants products as adjuvant therapy in the treatment of breast cancer

Conventional treatment of breast cancer may include surgery, radiation, chemotherapy and hormone therapy. The stage of diagnosis influences both the prognosis and the treatment strategies for breast cancer. Breast cancer is usually treated by combining surgery with radiation, chemotherapy and hormone therapy, whereby surgery is usually the first step in cancer treatment. However, the conventional treatment is often accompanied by severe side effects as nausea, fatigue, vomiting and hair loss. Furthermore, with patient survival rates increasing, oncologists and other therapists have to become more sensitive to the needs of breast cancer survivors that go beyond the mere alleviation of symptoms. A new trend in the breast cancer therapy is the combination of the conventional and complementary alternative medicine (CAM). Breast cancer survivors who combine the standard medicine, namely, chemotherapy and radiotherapy with the complementary are increasing. “Complementary” or “alternative” medicine refers to the methods advocated by other medical approaches, which include a multitude of diverse medical and health care systems, practices and products, not generally considered as part of conventional medicine. Among CAM used in cancer patients, herbal preparations or phytotherapy is the most commonly and the oldest used group of treatment (Ma et al., 2011). Generally, phytotherapeutic products were used as a combination therapy with the conventional chemotherapy to hopefully increase the therapeutic benefit and quality of life (QoL) as well as to decrease the side effects or complications of the conventional medicine. In the breast cancer domain, the biological effects of herbal medicinal products could be diverse such as (Nagykalnai et al., 2014) defence against

malignancy by increasing detoxification or cleaning, modification of the action of some hormones and enzymes, reduction in side effects and complications of chemotherapy and radiotherapy, and improvement of the function of the body's immune cells (i.e., stimulation of the production of cytokines including interleukin, interferon, tumour necrosis factor, and colony stimulating factor) (Rossi et al., 2015). Several commonly used herbs have been identified by the National Cancer Institute as possessing cancer-preventive properties. Those include members of the Allium sp. [garlic, onions and chives]; members of the Labiatae family [basil, mints, oregano, rosemary, sage, and thyme]; members of the Zingiberaceae family [turmeric and ginger]; members of the Umbelliferae family (anise, caraway, celery, chervil, cilantro, coriander, cumin, dill, fennel, and parsley) (Chan et al., 1993). In addition, many herbs contain a variety of phytosterols, triterpenes, flavonoids, saponins, and carotenoids, which have been shown from studies of legumes, fruit, and vegetables to be cancer chemoprotective (Nishimura et al., 1993). Vegetable and fruits have a high content of healthy components as vitamins, minerals, and fibers. Moreover, phytoconstituents resulting from the herbs such as *Vinca rosea, Taxus species, Allium sativum, Aloe vera, Angelica sinensis, Astragals membranaceus, Glycine max, Glycyrrhiza glabra, Hordeum vulgare, Hydrocotyle asiatica, Medicago sativa, Morinda citrifolia, Panax pseudoginseng, Saussurea lappa, Taxus wallichiana, Tinospora cordifolia, Viscum album, Withania somnifera, Zingiber officinale* etc. have been used in numerous preparations to improve function of the body's immune cells that stimulates production of cytokines including interleukin, interferon, tumor necrosis factor as well as colony stimulating factor. These preparations assist the body to battle cancer more efficiently and also decrease the harmful side effects of chemotherapy and radiotherapy (Sabarkar & Deshmukh, 2011). Compared to the Eastern part of the world where herbal treatments play a central role, they are not as popular in the United States and Europe. Such treatments form a complete medical system that is integrated in modern hospitals and clinics throughout most of Asia. Dobos et al. (2012) reported the practice of the concept of integrative oncology for breast cancer patients by German cancer centres such as the Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, academic teaching hospital of the University of Duisburg-Essen, and the Breast Centre at Kliniken Essen-Mitte (Dobos et al., 2017). In Africa, despite the heterogeneous nature of the continent and a deluge of informations on the composition and biological activity of many plant substances, to the best of our knowledge, few effort is devoted to the development of chemotherapeutic and prophylactic agents from plants. So, many breast cancer patients in Africa use plant products for self-medication.

2. Overview of selected plants with anti-breast cancer activities

Natural compounds with potent anti-cancer activities are widely available from different plant tissues. Eighty percent (80%) of the population worldwide traditionally use natural compounds contained in medicinal plants (Fulda, 2010). Therefore, investigations are being made to determine the anti-proliferative activity of many plant extracts. It has been found that a myriad of plant products exist that have shown very promising anti-breast cancer properties in vitro and in vivo. This is an overview of some selected plants with anti-breast cancer activities: *Vernonia amygdalina* (Thirumal et al.,2012), *Solanum torvum* (Nawal & Atta, 2013), *Avicennia marina* (Sharaf et al.,2000), *Annona muricata* (Olson, 2002), *Moringa Oleifera* (Al-Asmari et al., 2015), *Glycyrrhiza glabra* (Baltina, 2003) *and Curcuma longa* (Ranjbari et al., 2014).

2.1 *Vernonia amygdalina*

Vernonia amygdalina (*compositae*) is a small shrub that grows predominantly in the tropical Africa. The macerated leaves of the plant are used in making soup while the water extract serves as a tonic drink for the prevention of certain illnesses (Thirumal et al., 2012) . *Vernonia amygdalina* leaves (known as bitter leaf) were found to inhibit proliferation of breast cancer MCF-7 cells *in vitro* (Thirumal et al., 2012).

2.2 *Solanum torvum*

Solanum torvum (*S. Torvum*) belongs to *Solanaceae* (nightshade family) is a spiny herb or shrub 3-4 meters tall found throughout the tropical parts of India and in Andaman. Leaves, ovate, sinate or bilobed, lobes shallow, rarely deep, flowers white, in dense lateral racemes, berries globere, smooth, yellow or orangered, seeds smooth. The fruits and root extracts of *S. torvum* was found to be extremely effective in the prevention of cell proliferation of the mammary gland breast adenocarcinoma cell lines. The results obtained were compared with methotrexate-a known anticancer drug (Nawal & Atta, 2013). Moreover, Nunuk et al demonstrated that the ethyl acetat fraction of solanum torvum fruit has the best cytotoxic activity on T47D breast cancer cells (Nunuk et al., 2020).

2.3 *Avicennia marina*

Avicennia marina is specie of mangrove plants. Mangrove plants are halophyte plants resistant against sea salt. Mangrove is dominant specie in the Mangrove ecosystem. This plant is like a bush or shrub with a height of 1 to 10 meters. It has a white shell or gray or yellowish green, and its leaves are oval or sharp. Its flowers have 4 white or yellowish orange petals.

Flavonoid compounds of its leaf extract have anticancer effect on human breast cancer BT-20 cells (Sharaf et al., 2000).

2.4 *Annona muricata*

Annona muricata **(**common name: soursop) is a lowland tropical fruit-bearing tree in the Annonaceae family. Other common names are graviola and guanábana (sometimes shortened to guanába). Related species include *Annona cherimoya* and sugar-apple (*Annona. squamosa*), and paw paw (*Asimina triloba*). The soursop is native to tropical, Central and South America and the Caribbean, but is now widely cultivated in tropical areas worldwide, including southern Florida and Southeast Asia, from sea level to altitudes of around 1150 meters. Soursop has numerous traditional medicinal uses in South America and the Caribbean, and has become a popular nutritional medicinal supplement. Endrini et al., (2014) showed that the ethanolic extract of *Annona Muricata* leaves has potential cytotoxic effects on MCF-7 cells and that the effect increased with increased incubation time. The highest cytotoxic effect of this extract was displayed by the lowest IC50 value that has been achieved (Endrini et al., 2014).

2.5 *Moringa Oleifera*

Moringa oleifera L(MO) (Family: Moringaceae) is a perennial angiosperm plant, which includes several other species (Olson, 2002). It is a native of the Himalayan region that is widely cultivated throughout tropical and sub-tropical countries of the world including Saudi Arabia (Alaklabi, 2015; Mbikay, 2012). Study showed the remarkable effects of Moringa leaves and bark on MDA-MB-231, a ER-, PgR+ breast cancer cell line. The extracts of leaves and bark tested in a study induced a significant level of apoptosis (Al-Asmari et al., 2015).

2.6 *Glycyrrhiza glabra*

Glycyrrhiza glabra is wild plant from vegetables family, native to southern Europe, North Africa, and temperate regions of Asia. It grows in most parts of Iran, especially in the eastern and northeastern Khatam Marvast city and territories as well as Azerbaijan and Eghlid city. Glycyrrhizin is a triterpene glycoside that is the main compound in root extract and acts as an anti-proliferative agent against tumor cells, especially breast cancer cell line (MCF7) and HEP-2 and plays its role by inducing apoptosis (Baltina, 2003; Rossi et al., 2003).

2.7 *Curcuma Longa*

Curcuma longa is a plant from the Zingiberaceae family. This perennial plant usually requires humid and rainy environment. The main

habitat of *Curcuma longa* is hot areas of Asia such as India, Pakistan, Indonesia, and southern China, and it is native of Africa and South America. *Curcuma longa* has underground stem called rhizome. Several aerial shoots as high as 1 to 1.5 meters exit from these rhizomes (Fallah et al., 2010). Edible part of turmeric is dried rhizomes. The rhizome extract showed anti-proliferative and inhibitory effects of telomerase activity in breast cancer cell (Ranjbari et al., 2014).

Conclusion and perspectives

Phytotherapy is used as adjuvant therapy to conventional medicine in the treatment of breast cancer. Certain herbs defend the body from malignancy by augmenting detoxification or cleaning role of the body. Some biological response modifiers, derivatives of herbs, are recognized to hinder the growth of cancer by modifying the activity of precise hormones and enzymes, while other herbs diminish lethal side effects and complications of chemotherapy and radiotherapy (Sakarkar & Deshmukh, 2011). Different researches in vitro and in vivo have proved the anti-breast cancer activities of many medicinal plants as presented in this review. But, to the best of our knowledge, few effort has been made to pursue the research for their use as drug in the treatment of breast cancer. In Africa, the use of herbal products in the treatment of breast cancer still remains in the hands of traditional-practitioners, without any control of quality and efficacy. The major points blocking the use of phytotherapy in the 'modern medicine' generally and especially in the breast cancer treatment can be imputed to the lack of consistent and reliable sources of authentic medicinal plant materials. Species verification and authentication, cultivation using good agricultural practice protocols, and standardized/normalized methods and technology for plant extraction/mixture preparation. are often default. Furthermore, it lacks an definitions and routine preparation of the biochemical/biological ingredients and compositions of herbal medicines or the phytochemicals/phytocompounds derived from medicinal plants. Metabolite profiles, index compounds, and putative active compounds or metabolites are not identified; There are no adequate general and specific safety considerations, including tolerable high dosage, minimal effective dosage, and specific usage. Proof of efficacy in treating or assisting specific cancer patients is not existing as well as results/data from preclinical animal studies, execution of bona fide, and double-blind, placebo-included, statistician-assisted clinical trial studies and well-defined composition of herbal products (Fridlender et al., 2015).

Hence, efforts have to be made to create novel, improved, or modified clinical surveys, studies, and trial mechanisms that employ the stringent trial standards of the 21st century. Furthermore, they have also to

incorporate, at the international level, the wealth of old empirical but incomplete data from various records and documents accumulated by traditional medicine practices worldwide. This will help to expedit the discovery and development of new phytomedicines.. Africa continent represents one of the richest sources of biodiversity in the world. Herbal-based and plant-derived products could be exploited for the treatment of breast cancer.

Asknowledgement

The authors are very grateful to authors/editors/publishers whose articles, Journals and books were used as literature for this review article.

Authors contribution:

Conceptualization: AA Writting-Original draft preparation: AA Writting-review and editing: AA, JS Supervision: JS, CA, FG, CA

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